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Axillary Lymph Node Involvement in Stage III Breast Cancer: Treatment Implications

MIRANDA VOSS, FCS(SA),[1] JOHANN W. SCHNEIDER, MMed,[2] AND JUSTUS APFFELSTAEDT, FCS(SA)[1]*

[1]Department of Surgery, University of Stellenbosch, Tygerberg, South Africa
[2]Department of Anatomical Pathology, University of Stellenbosch, Tygerberg, South Africa

Background and Objectives: The introduction of multimodal therapy has improved the prognosis in stage III breast cancer. A knowledge of the likely axillary lymph node status at presentation is important, both to plan surgical therapy to the axilla and to establish the effect of induction therapy on the axillary nodes.

Methods: The study involved a chart review of 114 patients with stage III breast cancer who were treated by modified radical mastectomy without prior systemic therapy. A standard method was used for axillary dissection and numbers and levels of pathologically involved lymph nodes were recorded. The incidence of lymph node metastases was correlated with tumour size, grade, and clinical T stage. The accuracy of clinical axillary staging and the relationship between level III invasion and the number of level I and II nodes invaded was also assessed.

Results: Overall, 96 of 114 (84%) patients had axillary nodal metastases, and 37 of 114 (32%) patients had level III metastases. Eighteen of 43 tumours (42%) 30 mm or less had level III metastases and 27% of larger tumours had level III metastases (6/25 31−49-mm tumours, and 12/42 50+-mm tumours). Of 98 gradable cancers, only 1 out of 10 well-differentiated tumours had level III metastases, but the rate in moderately and poorly differentiated tumours was 36% (19/53) and 37% (13/35), respectively. Clinical node staging was unreliable. A group of patients with a low likelihood of level III metastases who might benefit from an axillary procedure less than level III dissection could not be identified preoperatively.

Conclusions: Patients with stage III breast cancer have a high incidence of level III axillary lymph node metastases. A subgroup with a low incidence of level III metastases could not be identified in this study. Until axillary downstaging has been convincingly demonstrated with induction therapy, a less than complete axillary procedure may leave the patient at high risk of axillary relapse.

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KEY WORDS: **breast; neoplasm staging; lymph node excision; surgery**

INTRODUCTION

In order to plan rational therapy of the axilla in breast cancer, a knowledge of the likelihood and levels of lymph node involvement is required [1,2]. Although this has been intensively studied in early breast cancer [3–10], few articles give this information for stage III [11] breast cancer, and differentiation by axillary level is not usually made [12,13]. Current recommendations for

*Correspondence to: Dr. J.P. Apffelstaedt, Department of Surgery, University of Stellenbosch, Tygerberg 7505, Cape Town, Republic of South Africa. Fax No.: 27 21 9337 999. E-mail: jpa@mweb.co.za

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treatment of stage III breast cancer involve the use of neoadjuvant therapy [14–17], but the effect of this therapy on downstaging the surgical specimen cannot be assessed without knowledge of the likely lymph node status at presentation. The present study records the numbers and levels of involved lymph nodes in patients with locally advanced breast cancer who did not receive prior systemic therapy.

PATIENTS AND METHODS

The study involved a review of the records at the Tygerberg Hospital Breast Clinic, Cape Town, South Africa, between January 1986 and September 1996. During this period, 3,006 new cases of breast cancer were diagnosed, of which 601 (20%) were stage III. Two hundred ninety-seven of these patients (49%) received surgical treatment.

Staging

Clinical staging was performed over this period by only two senior consultant surgeons according to the Union International Contre le Cancer/American Joint Committee on Cancer [11]. Staging included the routine use of chest X-ray, isotope bone scan, liver function tests, and imaging of the liver either by radionuclide scan or ultrasound to exclude metastatic disease.

Surgical Treatment

Patients were considered surgically resectable if all macroscopic tumour could be removed with or without the use of myocutaneous flaps to the mastectomy site. The surgical treatment was modified radical mastectomy including axillary clearance to level III, as described by Dao and Patel [18]. The mastectomy was performed from medial to lateral. Dissection further laterally along the margin of the pectoralis major was carried into the interpectoral tissue. With the pectoralis minor clearly visible, the tissue medial and lateral to the pectoralis minor muscle was marked by suturing beads to it at the medial and lateral margins of the muscle. The insertion of the pectoralis minor at the coracoid process was then divided, the muscle was mobilised medially, and the axillary dissection was carried out. Nodes medial to pectoralis minor were designated as level III, those behind pectoralis minor were designated as level II, and those lateral were designated as level I.

Pathological Method

The mastectomy specimens—level I, level II, and level III lymph nodes—were fixed separately in 10% buffered formalin. At least four representative sections were taken from each tumour. In addition, random sections were obtained from each quadrant of the breast, from the nipple, from all macroscopically abnormal areas at a distance from the main tumour, and from areas suspicious of cutaneous involvement. The individual groups of axillary lymph nodes were dissected and single sections from each macroscopic lymph node were submitted for histology. The tissue sections were processed and paraffin-embedded according to conventional techniques. Haematoxylin and eosin stains were performed on all sections.

The site, maximum diameter, World Health Organisation tumour type [19], degree of tumour differentiation according to Bloom and Richardson's criteria [20], and the presence or absence of lymphovascular invasion were determined in each breast tumour as part of a predesigned protocol.

The total number of lymph nodes as well as the numbers of lymph nodes involved by metastatic carcinoma were documented microscopically for each group of axillary lymph nodes in all cases. The absence or presence of extranodal invasion as well as carcinoma in soft tissue without identifiable remnants of lymph nodes was recorded.

Exclusions

Patients were excluded if their primary clinical assessment or surgical treatment had taken place outside Tygerberg Hospital. Also excluded were those in whom the clinical or pathological staging was inaccurate and those who had received preoperative radio- or chemotherapy. Patients who had started tamoxifen within 2 weeks before surgery were included.

RESULTS

Records were available for 259 of the 297 (87%) cases of stage III breast cancer operated between January 1986 and September 1996. Of these, 145 (56%) were excluded: 77 because of preoperative chemotherapy, 59 because patients had their primary treatment elsewhere, and nine because of inaccurate or incomplete files. One hundred fourteen records were studied. The average age of the patients was 57 years, and 39 (34%) of the patients were premenopausal. Ninety-six of the patients had invasive ductal carcinoma, seven had lobular, five had mucinous, two had medullary, one had papillary. Two were of mixed type: one of these was mixed ductal and lobular and one ductal and mucinous. One tumour was not specified.

Distribution of Tumours by Clinical Stage

The distribution of tumours by clinical stage is shown in Table I.

Mean Number of Nodes Sampled

Overall, the mean number of nodes sampled per case was 15.4. The mean number at level I was 8.2; at level II, 4.7; and at level III, 2.5.

TABLE I. Distribution of 114 Stage III Breast Cancers by Clinical Stage

Clinical stage of primary tumour	Clinical node stage		
	N0	N1	N2
T1	—	—	2
T2	—	—	14
T3	—	24	10
T4	7	35	22

Nodal Metastases

Overall, 96 patients (84%) had histopathological axillary lymph node involvement and 37 patients (32%) had positive nodes at level III. Of the node-positive patients, 55 of 96 (57%) had extracapsular invasion on histological examination.

The rate of pathologically infiltrated nodes is compared with clinical staging, size of tumour, and grade of tumour in Tables II, III, and IV. Clinical nodal staging is compared to pathological node status in Table V and the level III node status in relation to numbers of level I and II nodes involved is shown in Table VI.

Clinical Stage

T3 tumours had the lowest rate of level III metastases, but even in this group, nearly a quarter of the patients had level III lymph node metastases (Table II).

Size

In four patients, size was not recorded and the original pathological specimen was not available for review. Analysis of the remaining 110 cases showed that tumours of 3 cm or less had 42% (18/43) incidence of level III nodal metastases, which is a considerably higher rate than the incidence in the larger tumours. Tumours 31–49 mm and tumours of 50 mm and greater had rates of level III metastases of 24% (6/25) and 29% (12/42), respectively (Table III).

Pathological Grade

This was assessed for infiltrating ductal carcinoma (n = 96) or mixed tumours with a ductal component (n = 2) only. Moderately and poorly differentiated tumours showed a high incidence of nodal metastases and, in particular, a high incidence of level III metastases. Only 1 of the 10 patients with well-differentiated tumours had level III nodal metastases (Table IV).

Accuracy of Clinical Node Staging

Clinical node staging was inaccurate. Of the seven patients who had clinically disease-free axillae, five (71%) had nodal metastases and of the 48 patients with clinically matted nodes, 17 (35%) patients had metastases without extracapsular invasion and 2 (4%) had no nodal metastases (Table V).

TABLE II. Correlation Between Clinical and Histopathological Node Staging in Stage III Breast Cancer

Clinical stage of primary tumour	Patients with positive nodes according to axillary level		
	Level I (%)	Level II (%)	Level III (%)
T1, T2	16/16 (100)	9/16 (56)	8/16 (50)
T3	25/34 (74)	12/34 (35)	8/34 (24)
T4	52/64 (81)	34/64 (53)	21/64 (33)
Total	93/114 (82)	55/114 (48)	37/114 (32)

TABLE III. Percentage of Patients With Positive Nodes Vs. Size of Primary Tumour in 110 Stage III Breast Cancers

Size of primary tumour (mm)	Level I (%)	Level II (%)	Level III (%)
0–30	38/43 (88)	20/43 (47)	18/43 (42)
31–49	20/25 (80)	12/25 (48)	6/25 (24)
50+	32/42 (76)	21/42 (50)	12/42 (29)
Total	110	110	110

TABLE IV. Percentage of Patients With Positive Nodes Vs. Tumour Grade for 98 Gradable Stage III Breast Cancers*

Bloom and Richardson grade	Axillary level		
	Level I (%)	Level II (%)	Level III (%)
1	8/10 (80)	2/10 (20)	1/10 (10)
2	45/53 (85)	28/53 (53)	19/53 (36)
3	31/35 (89)	20/35 (57)	13/35 (37)
Total	98	98	98

*Ninety-six patients with infiltrating ductal carcinoma and two patients with mixed tumours.

Level III Lymph Node Involvement in Relation to Numbers of Level I and II Positive Nodes

The frequency of level III lymph node invasion increased dramatically with increasing number of involved nodes at levels I and II. Five of 46 (11%) of patients with one to four positive level I and II nodes had positive level III nodes, but this rose to 31 of 49 (63%) patients when more than four level I and II nodes were invaded. Interestingly, 1 of 19 patients (5%) had negative nodes at levels I and II nodes but had a positive node at level III (Table VI).

DISCUSSION

The 20% proportion of patients with stage III cancers in this series is higher than the 10%–15% quoted in series from Europe and the United States [21–23] and reflects the indigent, disadvantaged nature of our patient population.

TABLE V. Clinical Node Stage Vs. Pathological Node Stage in 114 Stage III Breast Cancers

Clinical node stage	Pathological node stage			Total
	pN0	pN1	pN2	
N0	2	2	3	7
N1	14	22	23	59
N2	2	17	29	48

TABLE VI. Level III Involvement in Relation to Number of Involved Nodes at Levels I/II in Stage III Breast Cancer

No. of positive nodes, levels I and II	No. of patients with positive nodes, level III (%)
0	1/19 (5)
1–4	5/46 (11)
>4	31/49 (63)

As expected in locally advanced disease [12], there was a high overall rate of incidence of nodal involvement and in particular, a high rate of level III involvement. The 57% incidence of extracapsular involvement is comparable to the 54% quoted in an unselected group of patients [24]. A study by Sacre [25] revealed erroneous clinical evaluation of the axilla in 39% of patients, and our results confirm the poor correlation between clinical and pathological staging. However, the clinical relevance of nonpalpable, pathologically involved nodes has been challenged [1].

Systemic induction therapy for stage III breast cancer has successfully downstaged the primary tumour, improving resectability rates [14] and in some cases allowing breast conservation [26,27]. It is hoped that new adjuvant therapies will effectively treat micrometastases and some studies have shown an improved long-term survival [28,29].

Surgical treatment of the axilla in breast cancer has two purposes: First, to provide prognostic information and direct adjuvant therapy; and second, to provide control of regional disease in the axilla. These factors must be weighed against the morbidity of the procedure, which is greater for a level III clearance than it is for a level I/II dissection. Mustard and Murillo [30] found that the incidence of lymphoedema decreased from 53% to 7% when the areolar tissue around the axillary vein was left intact. Whether a level I/II dissection provides adequate information on nodal status in early breast cancer has been the subject of extensive reviews, and the balance of evidence suggests that a level I/II dissection will correctly stage the axilla [2,31]. Multimodal therapy is now standard for patients with stage III breast cancer and as the pathological nodal status will not alter this, a level III dissection cannot be justified on prognostic grounds.

Of greater concern is the ability of a level I/II dissection to provide adequate regional control in a group of patients who, overall, have a 32% rate of pretreatment level III nodal metastases. A less than complete axillary procedure is associated with a higher rate of axillary failure [32–34]. Level III dissection is probably superior to radiotherapy in preventing axillary relapse [35], a miserable condition which is difficult to treat [36,37]. Our results show a high rate of level III lymph node metastases at presentation, occasionally even in well-differentiated tumours, and until nodal downstaging has been demonstrated following induction therapy we feel that a level III clearance offers the best prospect for axillary control.

CONCLUSION

Stage III breast cancers have a 32% overall rate of level III lymph node metastases. The highest rates were found in small tumours and poorly differentiated tumours, but a subgroup with a low rate of level III metastases could not be predicted in this study. Clinical axillary staging was unreliable and disease-free nodes at levels I and II did not predict disease-free level III nodes. Until axillary downstaging with neoadjuvant therapy has been demonstrated, a less than complete axillary treatment may leave the patient with a high risk of regional failure.

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